EXHIBIT A

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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/043,877	01/09/2002	Tapas Mukhopadhyay	INRP:095US 10200175	6285

7590 06/28/2004

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EXAMINER	
FETTEROLF, BRANDON J	
ART UNIT	**PAPER NUMBER**
1642	

DATE MAILED: 06/28/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

RECEIVED
Group Director
JUL 07 2004

Initial deadline for response to 3-month OA - 09-28-04
Final deadline for response to 3-month OA - 12-28-04

Client: INRP:095US
Assignee(s): SLH/MAD CPJ 7/12/04
Initials: dw SD

10200175

Office Action Summary	Application No.	Applicant(s)	
	10/043,877	MUKHOPADHYAY ET AL.	
	Examiner	Art Unit	
	Brandon J Fetterolf, PhD	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *31 March 2004*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-182* is/are pending in the application.

4a) Of the above claim(s) *4-8,11,30-74,78-82,107-160,163,166,168 and 171-175* is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *1-3, 9-10, 12-29, 75-77, 83-106, 161-162, 164-165, 167, 169-170, and 176-182* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☒ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's Election

The Election filed on 3/31/2004 in response to the Office Action of 2/27/2004 is acknowledged and has been entered. Applicant has elected without traverse Group I drawn to methods of administering a benzimidazole to a cell, as exemplified by claims 1-29, 75-106, 161-162, 164-167, and 169-182.

Claims 1-182 are currently pending.

Claims 4-8, 11, 30-74, 78-82, 107-160, 163, 166, 168, and 171-175 are withdrawn from consideration as being drawn to non-elected inventions and/or species.

Claims 1-3, 9-10, 12-29, 75-77, 83-106, 161-162, 164-165, 167, 169-170, and 176-182 are currently under consideration.

Species/Election

This application contains claims directed to the following patentably distinct species of the claimed invention: A method of treating a disease by administering an effective amount of a benzimidazole to a cell.

Applicant is required under 35 U.S.C. 121 to elect a single disclosed species for prosecution on the merits to which the claims shall be restricted if no generic claim is finally held to be allowable. Currently, claims 2, 11, 76, 166, 169 are generic to a number of different diseases (claims 11, 166) and a number of patentably distinct benzimidazole derivatives (claims 1, 76, 169).

Applicant is advised that a reply to this requirement must include an identification of the species that is elected consonant with this requirement, and a listing of all claims readable thereon, including any claims subsequently added. An argument that a claim is allowable or that all claims are generic is considered nonresponsive unless accompanied by an election.

Upon the allowance of a generic claim, applicant will be entitled to consideration of claims to additional species which are written in dependent form or otherwise include all the limitations of

an allowed generic claim as provided by 37 CFR 1.141. If claims are added after the election, applicant must indicate which are readable upon the elected species. MPEP § 809.02(a).

Should applicant traverse on the ground that the species are not patentably distinct, applicant should submit evidence or identify such evidence now of record showing the species to be obvious variants or clearly admit on the record that this is the case. In either instance, if the examiner finds one of the inventions unpatentable over the prior art, the evidence or admission may be used in a rejection under 35 U.S.C. 103(a) of the other invention.

During a telephone conversation with the applicant's representative, Sharon A. Bereford, on June 8, 2004 a provisional election of species was made without traverse to prosecute the species as cancer being the disease of interest and the benzimidazole derivative as mebendazole with the following R group substitution: R^3-benzoyl, R^2-H, and R^1-carbamate, claims 3, 77, and 170. *Applicant in replying to this Office action must make affirmation of this election.*

Claim Objections

Claim 161 is objected to because of the following informalities: Claim 161 is specifically drawn to a method for treating a patent with a hyperproliferative disorder comprising administering to said subject an amount of a benzimidazole effect to kill or inhibit the growth of hyperproliferative cells within said patient. The word "effect" does not appear to be used correctly. Appropriate correction is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 22-29, and 100-106 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

The term "status" of the tumor suppressor gene in Claims 12 and 100 is a relative term, which renders the claim indefinite. The term "status" is not defined by the claim and one of

ordinary skill in the art would not be reasonably apprised of the scope of the invention. The term "status" could imply activity, class, type, progress, ect.

Claim Rejections - 35 USC § 102

(a) the invention was known or used by others in this country, or patented or described in a printed publication in this or a foreign country, before the invention thereof by the applicant for a patent.

Claims 1-3, 9-10, 12-13, 19, 29, 75-77, 83-85, 92-99, 161-162, 164-165, 167, 169-170, and 176-182 are rejected under 35 U.S.C. 102(a) as being anticipated by Davis (WO 00/41669, 7/20/2000 IDS).

Claims 1-3, 9-10, 12-13, 19, 29, 75-77, 83-85, 92-99, 161-162, 164-165, 167, 169-170, and 176-182 are drawn to a method for inducing apoptosis in a cell expressing a tumor suppressor gene (claim 1-3, 9-10, 12-29) or a method of treating a patient having cancer (claim 75-77, 83-106) or a hyperproliferative disorder (claims 161-162), wherein the cancer cells express a tumor suppressor gene or inhibiting apoptosis or a method of inhibiting angiogenesis (claims 164-165, 167, 169-170, and 176-182) by administering an effective amount of a benzimidazole compound to a cell.

Davis teaches a method for treating cancer (page 11, line 14-15) and diseases associated with angiogenesis (page 2, line 8-10) involving administering 5(6)-substituted benzimidazole-2-carbamates to destroy newly formed vasculature. The patent further teaches that the disclosed benzimidazole of interest, mebendazole, reduced the vascular volume in CaNT tumour-bearing mice by 56% (page 13, Table 1). Further, Davis teaches various routes of administrating the compound i.e. oral, buccal, nasal, topical, rectal or parental (page 12, lines 6-9) and also, that the preferred daily dose may be in the range of 0.1 to 50mg/kg (page 12, lines 22). Although the reference does not specifically teach mebendazole inducing apoptosis in a cell expressing a tumor suppressor gene, the reference clearly teaches mebendazole as actively damaging vascular tissue, i.e. antiogenic. Thus, inherently, the loss of blood supply to the surrounding cells including cells expressing a tumor suppressor gene would inherently lead to cellular death or apoptosis due to lack of nutrients and oxygen. For example, the prior art teaches (page 1) that for a "solid tumour to grow it must develop its own blood supply

upon which it depends critically from the provision of oxygen and nutrients; if this blood supply is mechanically shut off the tumour undergoes necrotic death." In addition, the claimed functional limitation of a tumor cell expressing a tumor suppressor gene would be an inherent property of the tumor cell, as would be a tumor cell being multi-drug resistant. Thus, it does not appear that the claims language or limitations results in a manipulative difference in the method steps when compared to the prior art disclosure. See Bristol-Myers Squibb Company v. Ben Venue Laboratories 58 USPQ2d 1508 (CAFC 2001). The office does not have the facilities and resources to provide the factual evidence needed in order to establish that the product of the prior art does not possess the same material, structural and functional characteristics of the claimed product. In the absence of evidence to the contrary, the burden is on the applicant to prove that the claimed product is different from those taught by the prior art and to establish patentable differences. See In re Best 562F.2d 1252, 195 USPQ 430 (CCPA 1977) and Ex parte Gray 10 USPQ 2d 1922 (PTO Bd. Pat. App. & Int. 1989).

Hence, even though the claims are drawn to a mechanism by which angiogenesis is inhibited or cancer is treated by administration of mebendazole, the claimed method does not appear to distinguish over the prior art teaching of the same or nearly the same method. The mechanism of action does not have a bearing on the patentability of the invention if the invention was already known or obvious. Mere recognition of latent properties in the prior art does not render nonobviousness an otherwise known invention. In re Wiseman 201 USPQ 658 (CCPA 1979). Granting a patent on the discovery of an unknown but inherent function would remove from the public that which is in the public domain by virtue of its inclusion in, or obviousness from, the prior art. In re Baxter Travenol Labs, 21 USPQ2nd 1281 (Fed. Cir. 1991). See M.P.E.P. 2145.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-3, 9-10, 12-29, 75-77, 83-106, 161-162, 164-165, 167, 169-170, and 176-182 are rejected under 35 U.S.C. 103(a) as being unpatentable over Davis (WO 00/41669, 7/20/2000 IDS) in combination with Perdoma et al. (J. Cancer Res. Clin. Oncol. 1998, 124, 10-18) and Camden (US 6,262,093).

Davis teaches as set forth above with regard to claims 1-3, 9-10, 12-13, 19, 29, 75-77, 83-85, 92-99, 161-162, 164-165, 167, 169-170, and 176-182 a method for treating cancer (page 11, line 14-15) and diseases associated with angiogenesis (page 2, line 8-10) involving administering 5(6)-substituted benzimidazole-2-carbamates to destroy newly formed vasculature. The patent further teaches that the disclosed benzimidazole of interest, mebendazole, reduced the vascular volume in CaNT tumour-bearing mice by 56% (page 13, Table 1). Further, Davis teaches various routes of administrating the compound i.e. oral, buccal, nasal, topical, rectal or parental (page 12, lines 6-9) and also, that the preferred daily dose may be in the range of 0.1 to 50mg/kg (page 12, lines 22).

Davis does not teach determining the tumor suppressor status of the tumor cell prior to administration of the claimed benzimidazole derivative, mebendazole. In addition, Davis does not teach administering a benzimidazole to specific types of cancer i.e. a lung, non-small cell lung carcinoma, breast cancer, or sarcoma cell.

Perdoma teaches determining the p53 status, by Western blot analysis (page 12, 3rd paragraph) or other methods such as polymerase chain reaction (PCR), could make it possible to predict the response to therapy in certain patients (page 17, 1st column, 2nd paragraph). Perdoma further teaches that the response to cisplatin *in vivo* of NSCLC tumor lines was dependent on p53 status (page 17, 1st column, 2nd paragraph). Specifically, the reference teaches wt-p53 tumors showed a regression in size of around 60%, whereas mt-p53 tumors stopped growing (page 17, 1st column, 2nd paragraph).

Camden teaches methods of treating cancer using various benzimidazole derivatives (Title). The patent further describes cancer as all types of cancer or neoplasm or malignant tumors found in mammals, including carcinomas and sarcomas. Further, the reference teaches examples of cancer are cancer of the brain, breast, lung, non-small cell lung and sarcoma (column 3, line 45+).

It would have been *prima facie* obvious to one of ordinary skill in the art at the time the invention was made to administer mebendazole to various tumor cells such as lung, non-small-cell lung carcinoma, breast cancer, or sarcoma cell. One would have been motivated to make these

modifications because Davis teaches that the mebendazole can be used to treat cancer in general, while Camden teaches the administration of mebendazole-like compound (benzimidazole derivative) for specific cancers. Thus, one of ordinary skill in the art would have a reasonable expectation of success because the compounds of Camden and Davis are structurally similar. In addition, it would have been *prima facie* obvious to determine the status of a tumor suppressor gene, like p53, in a tumor cell prior to administering mebendazole using techniques such as Western blot, PCR or other methods of analysis. One would have been motivated to do so because Davis teaches administering mebendazole to mice bearing CaNT tumors, while Perdoma teaches that the "response to cisplatin *in vivo* of tumors derived from different NSCLC lines was dependent on p53 status (page 17, 1st column, 2nd paragraph)." Further, one of ordinary skill in the art would have a reasonable expectation of success because Perdoma teaches "analysis of p53 status, by immunohistochemical or other methods such as the polymerase chain reaction *(PCR)*, could make it possible to predict the response to therapy in certain patients (page 17, 1st column, 2nd paragraph)."

No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Brandon J Fetterolf, PhD whose telephone number is (571)-272-2919. The examiner can normally be reached Monday through Friday from 8:30 to 5:00.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Christina Chan can be reached on (571)-272-0841. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Brandon J Fetterolf, PhD
Examiner

Art Unit 1642

BF

GARY NICKOL
PRIMARY EXAMINER